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Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection

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ABSTRACT

Schizophrenia is a debilitating psychiatric condition often associated with poor quality of life and decreased life expectancy. Lack of progress in improving treatment outcomes has been attributed to limited knowledge of the underlying biology, although large-scale genomic studies have begun to provide such insight. We report a new genome-wide association study of schizophrenia (11,260 cases and 24,542 controls) and through meta-analysis with existing data we identify 50 novel associated loci and 145 loci in total. Through integrating genomic fine-mapping with brain expression and chromosome conformation data, we identify candidate causal genes within 33 loci. We show for the first time that the common variant association signal is highly enriched among genes that are under strong selective pressures. These findings provide novel insights into the biology and genetic architecture of schizophrenia, highlight the importance of mutation intolerant genes and suggest a mechanism by which common risk variants persist in the population.

Schizophrenia is characterised by psychosis and negative symptoms such as social and emotional withdrawal. While onset of psychosis typically does not occur until late adolescence or early adult life, there is strong evidence from clinical and epidemiological studies that schizophrenia reflects a disturbance of neurodevelopment[1]. It confers substantial mortality and morbidity, with a mean reduction in life expectancy of 15-30 years[2,3]. Although recovery is possible, most patients have poor social and functional outcomes[4]. No substantial improvements in outcomes have emerged since the advent of antipsychotic medication in the mid-20th century, a fact that has been attributed to a lack of knowledge of pathophysiology[1].

Schizophrenia is both highly heritable and polygenic, with risk ascribed to variants spanning the full spectrum of population frequencies[5-7]. The relative contributions of alleles of various frequencies is not fully resolved, but recent studies estimate that common alleles, captured by genome-wide association study (GWAS) arrays, capture between a third and a half of the genetic variance in liability[8]. There has been a long-standing debate, from an evolutionary standpoint, as to how common risk alleles persist in the population, particularly given the early mortality and decreased fecundity associated with schizophrenia[9]. Various hypotheses have been proposed including compensatory advantage (balancing selection), whereby schizophrenia alleles confer reproductive advantages in particular contexts[10,11]; hitchhiking, whereby risk alleles are maintained by their linkage to positively selected alleles[12]; or contrasting theories that attribute these effects to rare variants and gene-environment interaction[13]. Addressing these competing hypotheses is now tractable given advances from recent studies of common genetic variation in schizophrenia.

The largest published schizophrenia GWAS, that from the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC), identified 108 genome-wide significant (GWS) loci and unequivocally demonstrated the value of increasing sample sizes for discovery in schizophrenia genetics research[5]. Here, we report a large, phenotypically homogeneous GWA

study of schizophrenia which, when combined with previous published data, identifies novel facets of genetic architecture and biology, and demonstrates that the evolutionary process of background selection can explain the persistence of common risk alleles in the population.

RESULTS

GWAS and Meta-analysis

We obtained genome-wide genotype information for schizophrenia cases from the UK (the CLOZUK sample), which we combined with control datasets obtained from public repositories or through collaboration. The final sample size was of 11,260 cases and 24,542 controls (5,220 cases and 18,823 controls not in previous schizophrenia GWAS**; Methods**; **Supplementary Figure 1**; **Supplementary Figure 2**). At a genome wide level, the association statistics indicated that the common variant architecture in the CLOZUK sample was highly correlated with an independent sample of 29,415 cases and 40,101 controls from the PGC (genetic correlation = 0.954±0.030; $p=6.63x10^{-227}$) and this was further confirmed by polygenic risk score and trend test analyses across the datasets at a range of association p-value thresholds (**Methods** and **Supplementary Table 1** and **2).**

Meta-analysis of the CLOZUK and the independent PGC dataset, excluding related and overlapping samples (total 40,675 cases and 64,643 controls; **Supplementary Figure 1**), identified 179 independent GWS SNPs ($p<5x10^{-8}$, **Supplementary Table 3**) mapping to 145 independent loci (**Methods, Figure 1, Supplementary Table 4**). The 145 associated loci include 93 of those that were GWS in the study of the PGC, the majority of which showed a strengthened association **(Supplementary Figure 4, Supplementary Table 5)**. This does not imply the remaining 15 PGC loci were false positives, rather this reflects the expected inflation of effect sizes for GWS SNPs in incompletely powered studies, and as we

demonstrate, is consistent with all 108 PGC loci representing true positives (see **Supplementary Note**). Of the 52 loci not identified by the PGC, two have been reported as genome-wide significant in other studies: the locus at ZEB2[14] and a locus on chromosome 8 (38.0-38.3 MB)[15].

In further independent samples (5,662 cases and 154,224 controls); 43 of the 50 GWS index SNPs showed the same pattern of allelic association, a level that far surpasses chance ($p=1.05x10^{-7}$). Despite the modest number of cases in these samples, 18 of the 50 index alleles reached nominal significance ($p<0.05$), again implausible by chance ($p=1.46x10^{-11}$). None demonstrated evidence for heterogeneity of effect (**Methods**, **Supplementary Table 6**).

Mutation intolerant genes

Recent studies have shown that mutation intolerant genes capture much of the rare variant architecture of neurodevelopmental disorders such as autism, intellectual disability and developmental delay as well as schizophrenia[16-19]. Here, we show that for schizophrenia, this also holds for common variation. Using gene set analysis in MAGMA[20], loss-of-function (LoF) intolerant genes (N=3,230) as defined by the Exome Aggregation Consortium (ExAC)[21] using their gene-level constraint metric pLI ≥ 0.9, were enriched for schizophrenia common variant associations in comparison with all other annotated genes ($p=4.1x10^{-16}$).

It has been shown that pLI is correlated with gene expression across tissues, including brain[21], which raises the possibility that the LoF-intolerant gene enrichment in schizophrenia may reflect enrichment for signal in genes expressed in the brain. However, LoF-intolerant gene set enrichment was robust to the inclusion of "brain expressed" (N=10,360) and "brain specific" (N=2,647) gene sets[19] as covariates in the analysis ($p=1.89x10^{-10}$) or to controlling for FPKM gene expression values ($p=1.03x10^{-14}$) in brain[22] .

It has been suggested that clustering of risk alleles in mutation intolerant genes is a hallmark of early-onset traits under natural selection[23,24]. However, LoF-intolerant genes are known to be enriched for SNPs identified as genome-wide significant in GWAS studies (as listed in the NHGRI-EBI GWAS Catalog[25]) and for broad categories of disorders[21]. To examine whether our finding is a property of polygenic disorders in general, we obtained summary genetic data from a neuropsychiatric and non-psychiatric late-onset disorder (Alzheimer's disease, type-2 diabetes) and a psychological trait (Neuroticism), each of which has been shown to be under minimal selective pressure (see **Methods**). These other phenotypes show at best a weak signal for enrichment of the LoF-intolerant gene set in the MAGMA analysis, not comparable to that seen in schizophrenia (Alzheimer's disease p=0.008, type-2 diabetes p=0.016, Neuroticism p=0.066).

To quantify the contribution of SNPs within LoF-intolerant genes to schizophrenia SNP-based heritability (h^2_{SNP}) we used partitioned LDSR[26] (**Supplementary Table 7)**. Overall, genic SNPs account for 64% of h^2_{SNP}, a 1.23-fold enrichment proportional to their SNP content ($p=5.93x10^{-14}$). Consistent with the analysis using MAGMA, h^2_{SNP} was enriched in LoF-intolerant genes (2.01-fold; $p=2.78x10^{-24}$), which explained 30% of all h^2_{SNP} (equating to 47% of all genic h^2_{SNP}). In contrast, genes classed as non LoF-intolerant (pLI<0.9) were significantly depleted for h^2_{SNP} relative to their SNP content (0.90-fold; $p=5.86x10^{-3}$), although in absolute terms, SNPs in these genes accounted for 34% of h^2_{SNP}. A finer scale analysis of the relationship between LoF intolerance scores and enrichment for association showed that enrichment is restricted to genes with a pLI score above 0.9, precisely those defined as "LoF-intolerant" **(Supplementary Figure 5)**.

Common risk alleles in regions under background selection

Our finding that LoF-intolerant genes are enriched for common risk variants raises the question of how such alleles are found at common frequencies in the population. While the

contribution of ultra-rare variation in functionally important genes to disorders associated with low fecundity can be accounted for by *de novo* mutation[16,19,27], this cannot explain the persistence of common alleles. To address this question, we used partitioned LDSR to test the relationship between schizophrenia associated alleles and SNP-based signatures of natural selection. These included measures of positive selection, background selection, and Neanderthal introgression. We examined the heritability of SNPs after thresholding them at extreme values for these metrics (top 2%, 1% and 0.5%), including in the baseline model annotation sets such as LoF-intolerant genes and genomic regions with extreme linkage disequilibrium patterns **(Methods)**.

We observed strong evidence for schizophrenia h^2_{SNP} enrichment in SNPs under strong background selection (BGS), which was consistent across all the thresholds we examined (**Table 1**). We also found a significant depletion of h^2_{SNP} in SNPs subject to positive selection as indexed by the CLR statistic. These two results are mutually consistent, as the calculation of the CLR statistic explicitly controls for the effect of BGS[28]. This suggests that SNPs under positive selection, but under weak or no BGS, are depleted for association with schizophrenia. No significant relationship between h^2_{SNP} and other positive selection or Neanderthal introgression measures was found after correction for multiple testing **(Table 1)**. An LDSR analysis treating BGS measures as a quantitative trait, rather than as a binary one, confirmed that the relationship between BGS and schizophrenia association was not due to the imposition of arbitrary thresholds to define strong BGS ($p=7.73x10^{-11}$). We also note that the τ_c statistic of the LDSC model is significant for BGS, in both binary (p=0.041) and quantitative (p=0.023) analyses (**Supplementary Table 8)**. The τ_c statistic indicates the enrichment of BGS after controlling for all other annotations in the model (including LoF-intolerant genes)[26], and thus represents a robust and conservative test for the BGS enrichment.

The above analyses accounts for a possible confounding relationship between LoF intolerance and BGS. To illustrate this more clearly, we binned the BGS intensities into four categories of increasing score, and classified SNPs in these bins according to whether they are in LoF-intolerant genes, "all other" genes sets and a non-genic set **(Supplementary Figure 6)**. Note that the lower boundary of the top bin (BGS intensity > 0.75) corresponds approximately to the top 2% BGS threshold in **Table 1** and is equivalent to a reduction in effective population size estimated at each SNP of 75% or more[29]. We found significant heritability enrichment across all BGS intensity intervals in LoF-intolerant genes that increased progressively with higher intensity scores. Importantly, we also found heritability enrichment for SNPs under BGS pressure in genes that are not LoF intolerant, restricted to the highest BGS intensity bin. Indeed the highest BGS intensity bin in non-LoF genes was enriched for heritability at a level roughly equivalent to all LoF genes. These findings point to BGS and LoF intolerance as making at least partially independent contributions to heritability enrichment in schizophrenia. In contrast, none of the phenotypes we selected on the basis of their minimal impact on fecundity (Alzheimer's disease, type-2 diabetes, neuroticism) showed significant BGS enrichment for heritability using either the BGS τ_c statistic of the LDSC model (minimum $p > 0.24$), or when specifically testing regions of high BGS intensity in genes that are tolerant (pLI<0.9) of functional mutations (minimum $p > 0.40$).

Systems genomics

Using MAGMA, we undertook a primary analysis of 134 central nervous system related gene sets we have previously shown captures the excess CNV burden in schizophrenia[30]. In a GWAS context, we now show that collectively, this group of gene sets captures a disproportionately high fraction of h^2_{SNP} (30% of total heritability; enrichment =1.63; $p= 8.57x10^{-13}$; 46% of genic heritability; **Supplementary Table 8**). Of the 134 sets, 54 were nominally significant of which 12 survived multiple-testing correction (family-wise error rate

(FWER) $p < 0.05$, **Supplementary Table 9**), with no notable association for gene sets such as the ARC protein complex and NMDAR protein network, that we have previously implicated in rare variant studies[30,31]. Stepwise conditional analysis, adjusting sequentially for the more strongly associated gene sets, resulted in six gene sets that were independently associated with schizophrenia (**Table 2** and **Data Supplement**). These extend from low-level molecular and sub-cellular processes to broad behavioural phenotypes. The most strongly associated gene set is constituted by the targets of the Fragile X Mental Retardation Protein (FMRP)[32]. FMRP is a neuronal RNA-binding protein that interacts with polyribosomal mRNAs (the 842 target transcripts of this gene set[32]) and is thought to act by inhibiting translation of target mRNAs, including many transcripts of pre- and post-synaptic proteins. The FMRP target set has been shown to be enriched for rare mutational burden in *de novo* exome sequencing studies of autism[33] and intellectual disability[31]. In schizophrenia studies, it has also been shown to be nominally significantly enriched for association signal in sequencing studies[8,31] and in GWAS[5,8] but only inconsistently in studies of copy number variation[30,34]. Here we provide the strongest evidence to date for the enrichment of this gene set in schizophrenia.

We highlight another five gene sets that are independently associated with schizophrenia. Three of these derive from the Mouse Genome Informatics database[35] and relate to behavioural and neurophysiological correlates of learning; Abnormal Behaviour (MP:0004924), Abnormal Nervous System Electrophysiology (MP:0002272) and Abnormal Long Term Potentiation (MP:0002207). We note that two of these gene sets (MP:0004924 and MP:0002207) were among the five most enriched of 134 gene sets tested in a recent schizophrenia CNV analysis[30]. The remaining two independently associated genes sets were voltage-gated calcium channel complexes[36] and the 5-HT_{2C} receptor complex[37]. The calcium channel finding confirms extensive evidence from common and rare variant studies

implicating calcium channel genes in schizophrenia[5,8], including a novel GWAS locus in *CACNA1D* identified in our meta-analysis. Whilst there is less convergent evidence in support of the involvement of the 5-HT_{2C} receptor complex in schizophrenia, the fact that we identify independent association for this gene set implicates these genes in schizophrenia pathophysiology and potentially rejuvenates a previous avenue of 5-HT_{2C} ligand therapeutic endeavour in schizophrenia research[38]. However we interpret this result with caution given the small size of this gene set and the fact that a number of its genes encode synaptic proteins that are structurally related to other receptor complexes[37], not only 5-HT_{2C}.

Systems genomics and mutation intolerant genes

The LoF-intolerant genes and the six conditionally independent ("significant") CNS-related gene sets together account for 39% of schizophrenia SNP-based heritability ($p=5.07x10^{-26}$), equating to 61% of genic heritability **(Figure 2A; Supplementary Table 7)**. This is likely to be an underestimation of the true effect of these gene sets since distal non-genic regulatory elements (not included in this analysis) will add to the heritability explained by these genes. In examining the relationship between the LoF-intolerant and CNS-related gene sets **(Figure 2A)**, genes belonging to both categories were the most highly enriched (2.6-fold; $p=7.90x10^{-15}$), although LoF-intolerant genes that were not annotated to our significant CNS gene sets still displayed enrichment for SNP-based heritability (1.74-fold; $p=9.77x10^{-10}$), while genes that were in the significant CNS gene sets but had pLI<0.9 showed more modest enrichment (1.39-fold; $p= 6.05x10^{-4}$). Notably genes outside these categories were depleted in heritability relative to their SNP content (enrichment=0.79, $p=1.82x10^{-7}$).

This general pattern remained when we focussed on the six significant CNS gene sets individually, in that the enrichment in these gene sets derives primarily from their intersection with LoF-intolerant genes **(Figure 2B)**. Indeed, only the targets of FMRP showed significant enrichment for SNPs in genes that are not LoF intolerant (2.06-fold; $p=4.23x10^{-5}$).

Data-driven gene set analysis

To set the systems genomics results in context, and to ensure we were not missing enrichment in other gene sets by our hypothesis driven approach, we undertook a purely data-driven analysis of a larger comprehensive annotation of gene sets from multiple public databases, totalling 6,677 gene sets **(Methods, Supplementary Table 10**). Six gene sets survived FWER correction for the full 6,677 gene sets and showed independence through conditional analyses. The LoF-intolerant gene set was the most strongly enriched followed by the two most strongly associated functional gene sets we had specified in our hypothesis-driven CNS gene set analysis (FMRP targets and MGI Abnormal Behaviour genes). The other three sets were calcium ion import (GO:0070509), membrane depolarisation during action potential (GO:0086010) and synaptic transmission (GO:0007268). These are highly overlapping with the independently associated sets from our primary CNS systems genomic analysis. Indeed if we repeat the data-driven comprehensive gene set analysis whilst adjusting for the six independently associated CNS gene sets, then the only surviving enrichment term is the LoF-intolerant genes. These results are consistent with those from CNV analysis[30] in that they do not support annotations other than those related to CNS function, and demonstrate that hypothesis based analysis to maximise power does not substantially impact on the overall pattern of results.

Identifying likely candidates within associated loci

To identify SNPs and genes which might be causally linked to the GWS associations, we used FINEMAP[39] to identify credibly causal alleles (those with a cumulative posterior probability for a locus of at least 95%) and functionally annotated these alleles using ANNOVAR[40]. This identified 6,105 credible SNPs across 144 GWS loci, excluding the MHC region (**Methods**, **Supplementary Table 11**). From these, we defined a highly credible set of SNPs (N=25) as those that are more likely to explain the associations than all other

SNPs combined (i.e. with a FINEMAP posterior probability greater than 0.5). Of these, 14 mapped to genes based on putative functionality (exonic SNPs that cause non-synonymous or splice variations or promoter SNPs, n=6) or mapped to regions identified as likely regulatory elements (n=8) through chromosome conformation analysis performed in tissue from the developing brain using Hi-C[41] physical interactions (**Methods; Supplementary Table 12**). One of the implicated alleles is a nonsynonymous variant in the manganese and zinc transporter gene *SLC39A8*. Nonsynonymous variants in this gene have been associated with severe neurodevelopmental disorders and deficiencies of SLC39A8 with related impaired glycosylation[42], highlighting a mechanism of therapeutic potential.

We also applied Summary-data based Mendelian Randomisation (SMR) analysis[43] to the data in concert with the dorsolateral prefrontal cortex eQTL data from the CommonMind Consortium[44] aiming to identify variants that might be causally linked through expression changes of specific genes. (**Methods**, **Supplementary Table 13**). After applying a conservative threshold ($p_{HEIDI}>0.05$) which prioritises those co-localised signals due to a single causal variant[43], we identified 22 candidates at 19 loci with a false discovery rate $p<0.05$.

In total, the combination of FINEMAP, Hi-C and SMR analyses assigned potentially causal genes at 33 GWS loci and implicated a single gene at 27 of these loci. However, the analyses intersect for a single gene, ZNF823, indicating the need for more comprehensive functional genomic annotations in CNS relevant tissues.

DISCUSSION

In the largest genetic study of schizophrenia to date, we explore the genomic architecture of, and the evolutionary pressures on, common variants associated with the disorder. Our study

provides the first evidence linking common variation in LoF-intolerant genes to risk of developing schizophrenia and demonstrates that these genes account for a substantial proportion (30%) of schizophrenia SNP-based heritability. Systems genomic analysis highlights six gene sets that are independently associated with schizophrenia, and point to molecular, physiological and behavioural pathways involved in schizophrenia pathogenesis.

Given mutation intolerance is due to high selection pressure[21,23,24], our finding that schizophrenia risk variants that persist at common allele frequencies are enriched in loss-of-function intolerant genes might appear counter-intuitive. However, novel evidence presented here suggests this can be reconciled by background selection (BGS) which is a consequence of purifying selection in regions of low recombination[45,46]. In such regions, recurrent selection against deleterious variants causes haplotypes to be removed from the gene pool, which reduces genetic diversity in a manner equivalent to a reduction in effective population size[47]. This in turn impairs the efficiency of the selection process, allowing alleles with small deleterious effects to rise in frequency by drift[48]. Such a consequence of purifying selection has been shown to be compatible with the genomic architecture of complex human traits[49] and to influence phenotypes in model organisms[50]. We have explicitly modelled this effect (both theoretically and via simulations; **Supplementary Note**) and provide strong evidence for the feasibility of this effect as explanatory for the effect sizes seen for common alleles in schizophrenia.

We did not find enrichment for any measure of positive selection or Neanderthal introgression. A recent study explained a negative correlation between schizophrenia associations and metrics indicative of a Neanderthal selective sweep as evidence for positive selection or polygenic adaptation in schizophrenia[12]. We do not find any significant correlation in our model, which addresses the contribution of BGS, and hence our results are not consistent with large contributions of positive selection to the genetic architecture of

schizophrenia (**Table 1**). Indeed positive selection is not widespread in humans, as reported by other studies that explicitly considered or accounted for BGS[28,51]. Polygenic adaptation, the co-occurrence of many subtle allele frequency shifts at loci influencing complex traits[52], remains an intriguing possibility, but has not been implicated in psychiatric phenotypes, including schizophrenia, in recent analyses[53,54]. In contrast, BGS has been proposed as a mechanism driving Human-Neanderthal incompatibilities, as regions with stronger estimated BGS have lower estimated Neanderthal introgression[55]. We therefore conclude that the bulk of the BGS signal we obtain is unlikely to be influenced by positive selection[29], challenging theories of selective advantage of schizophrenia risk alleles to explain their high population frequencies.

AUTHOR CONTRIBUTIONS

A.F.P. curated and processed genetic data, performed statistical analyses, contributed to the interpretation of results and participated in the primary drafting of the manuscript.

P.H., A.J.P., V.E-P., A.C. and E.S. performed statistical analyses, contributed to the interpretation of results and participated in the primary drafting of the manuscript.

S.R. curated and processed genetic data and participated in the primary drafting of the manuscript.

N.C. and M.L.H. contributed to the interpretation of results and participated in the primary drafting of the manuscript.

S.E.L., S.B. and A.L. participated in the recruitment of participants for the study and curated and managed their phenotypic information.

D.C., J.H, L.H, E.R. and G.K. contributed and curated data used in the statistical analyses.

K.M. managed the laboratory and genotyping procedures in Cardiff University.

J. H. M, D. A. C. and D.R. supervised the recruitment of the participants for the study.

S. A. M. managed the genotyping of samples for the study.

N. R. W. contributed genotypes of control samples and participated in the primary drafting of the manuscript.

D.H. G, L. M. H., D. M. R., P. S., E. A. S. and H.W. performed statistical analyses and contributed to the interpretation of results.

M. J. O. and M. C. O'D. conceived and supervised the project, contributed to the interpretation of results and participated in the primary drafting of the manuscript.

J. T. R. W. conceived and supervised the project, led the recruitment of the participants and sample acquisition for the study, performed statistical analysis, contributed to the interpretation of results and participated in the primary drafting of the manuscript.

All other authors contributed genotypes of control samples or summary statistics of replication samples.

All authors had the opportunity to review and comment on the manuscript and all approved the final manuscript.

COMPETING FINANCIAL INTERESTS

D. A. C. is a full-time employee and stockholder of Eli Lilly and Company. The remaining authors declare no conflicts of interest.

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